REMARKS

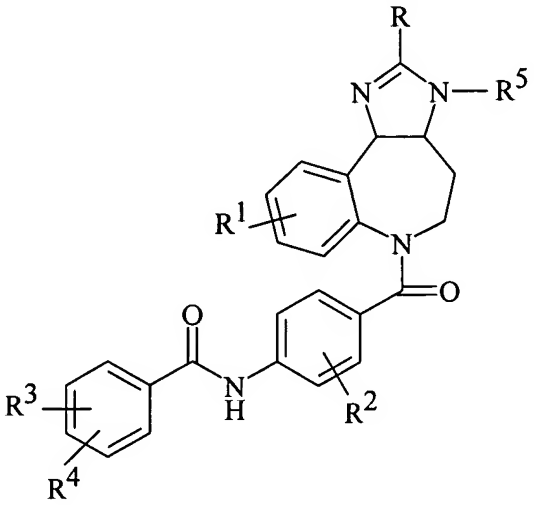
Claims 1-15 were pending in the above-identified application prior to entry of this Amendment. In this Amendment, claims 1 and 2 have been cancelled. Claims 3-15 have been amended. Accordingly, after entry of this Amendment, claims 3-15 are pending in this case. The changes to the claims do not constitute the addition of new matter and full support for the changes may be found in the specification and claims as originally filed.

Rejection Under 35 U.S.C. §102(e)

The examiner has rejected claims XX under 35 U.S.C. §102(a) as allegedly anticipated by Ellis-Grosse et al. (U.S. Patent No. 6,420,358, the '358 patent). This rejection is respectfully traversed.

As stated in the '358 patent, "[T]his invention relates to new methods of increasing urine flow in humans while controlling the loss of electrolytes, the method comprising administering N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11)ylcarbonyl)-3-chlorophenyl]-5-fluoro-2-methylbenzamide (or a pharmaceutically acceptable salt thereof) and a diuretic, such as furosemide."

The present invention, as defined by the currently amended claims, relates to a pharmaceutical composition comprising an effective amount of a diuretic agent and an effective amount of a vasopressin antagonist of Formula I.



I

N-[4-(5H-pyrrolo[2,1-c][1,4]benzodiazepin-10(11)ylcarbonyl)-3-chlorophenyl]-5-fluoro-2-methylbenzamide does not fall within the scope of Formula I. Therefore, it is respectfully submitted that the '358 patent fails to teach each and every limitation of the presently claimed invention and is not anticipatory.

In view of these amendments and remarks, withdrawal of the rejections under 35 U.S.C. §102(e) is respectfully requested.

Rejection Under 35 U.S.C. §103

The examiner has rejected claims 1-15 under 35 U.S.C. §103 as allegedly obvious in light of Ellis-Grosse et al. (U.S. Patent No. 6,420,358, the '358 patent), in view of Tanaka et al. (U.S. Patent No. 5,723,606, the '606 patent), This rejection is respectfully traversed.

The Examiner has stated that "[T]he difference between the above and applicants' claimed subject matter lies in that Ellis-Grosse et al. fail to highlight the use of the vasopressin antagonists as represented by the formula of present claim 3, or the specific vasopressin antagonist conivaptan." The Examiner goes on to state that "to the skilled artisan, applicants' claimed subject matter would have been obvious because Tanaka et al. teach compounds of the formula of present claim 3 (column 2, line 11 - column 12, line 26), and specifically conivaptan (column 74, line 1-25) as being effective as vasopressin antagonists (see the abstract) and useful for the management of heart failure, edema (column 28, lines 43,44 and 49)."

One of skill in the art would not have been motivated by the teaching of Ellis-Grosse to use the compounds disclosed in Tanaka in combination with a diuretic in order to arrive at the presently claimed invention. The presently claimed invention establishes that the aquaretic effects of conivaptan not only persist but are amplified with concurrent use of a loop diuretic (see the data shown in Figures 1 and 2 and in Table 1). This surprising result establishes synergism between the two drugs on urinary water excretion. In addition, the results of urinary sodium excretion shown in Figure 3 and in Table 1 below establish that combination therapy lessens the loss of sodium in the urine, particularly as the dose of furosemide is increased. This surprising result renders the claimed combination particularly useful in treatment or prevention of hyponatremia in edematous states like CHF in which therapy with a diuretic is standard care.

Additionally, the results on urinary potassium excretion shown in Figure 4 establishes that the combination substantially reduces potassium loss, particularly as the dose of furosemide is increased. This surprising result indicates the claimed combination is especially useful in treatment or prevention of hypokalemia in edematous states like CHF in which therapy with a diuretic is standard care.

In contrast Ellis-Grosse, with respect to the Rat study, states that "[B]oth V and F caused similar increases in urine flow rate (5.26.+-.1.13 to 19.51.+-.3.80 and 3.74.+-.0.18 to 17.02.+-.4.86 .mu.l/min, respectively). The combination did not have additive effect (V/F 4.03.+-.10.15 to 24.7.+-.6.05 μl/min). V and F decreased urine osmolality to a similar extent (V 1456.+-.166 to 571.+-.145, F 1515.+-.96 to 699.+-.69 mOsm/kg) while the combination caused a slightly larger decrease (1507.+-.84 to 396.+-.31 mOsm/kg). V caused a similar aquaresis in the presence and absence of F, as indicated by similar increases in free water clearance (V -17.31.+-.1.84 to -6.96.+-.5.17 and V/F -16.48.+-.1.04 to -4.89.+-.1.58 μl/min). F caused a similar natriuresis in the presence and absence of V. Na^+ excretion was increased from 0.09.+-.0.02 to 1.77.+-.10.60 with F and from 0.10.+-.0.02 to 1.11.+-.0.43 μEq/min with V/F. V alone caused a much smaller increase in Na^+ excretion (0.10.+-.0.02 to 0.67.+-.0.34 μEq/min)." (column 7, lines 36-52)

Additionally, Ellis-Grosse, with respect to the Human study, states that "[T]he 0 to 4 h urinary excretion of sodium, potassium , chloride and magnesium was significantly less with VPA-985 alone than with VPA-985 and furosemide administered concomitantly. No differences were observed in 0 to 24 h urinary excretion of potassium or magnesium between furosemide alone and coadministration with VPA-985. Mean serum sodium values 0 to 4 hours after the dose were increased by 2 mmol/L with VPA-985 alone and 3 mmol/L with furosemide administered concomitantly. VPA-985 did not alter serum potassium. A significant decrease in serum potassium was observed after furosemide alone (from 4.2 mmol/L at 0 h to 3.9 mmol/L at 4 hours after the dose), but the decrease was less after coadministration with VPA-985 (from 4.1 mmol/L at 0 hour to 4.0 mmol/L at 4 hours post dose. A similar trend was observed with serum chloride." (column 8, line 65 to column 6, line 12)

Therefore, Ellis-Grosse only discloses that "furosemide administered with VPA-985 increases urine flow and still maintains *some* electrolyte-sparing capabilities (emphasis added)." There is no teaching or suggestion that the combination of a diuretic and a vsopressin antagonist

of Formula I, as presently claimed, would have the synergistic effect on urinary water excretion. and urinary sodium excretion as presently demonstrated. Given that Ellis-Grosse only teaches that furosemide administered with VPA-985 increases urine flow and still maintains only some electrolyte-sparing capabilities, one of skill in the art would not have been motivated to combine the vasopressin antagoinists as disclosed in Tanaka with a diuretic in order to product the synergistic effects on urinary water excretion. and urinary sodium excretion as presently demonstrated.

In view of these amendments and remarks, withdrawal of the rejections under 35 U.S.C. §103 is respectfully requested.

Rejection Under 35 U.S.C. §112, First Paragraph

The examiner has rejected claims 7 and 8 as allegedly failing to meet the enablement /written description requirement of 35 U.S.C. §112, first paragraph.

Applicants respectfully disagree with the Examiner's contention that "[T]he term "prevention" or "preventing" is synonymous with the term "curing" ..." The terms preventing or prevention relate to stopping something from happening, especially by advance planning or action. In the present case the term preventing relates to the act of stopping the occurrence of a disease state. The term curing relates to the restoration of health and/or the recovery from disease. Therefore, as one term relates to stopping the occurrence of a disease state the other relates to ending a disease state and the restoration of health the terms "prevention" or "preventing" are not synonymous with the term "curing."

In order to expedite prosecution, claims 7 and 8 have been amended to recite a method for treating congestive heart failure and other edematous conditions in a mammal comprising administering an effective amount of a pharmaceutical composition of claim 3.

In view of these amendments and remarks, withdrawal of the rejections under 35 U.S.C. §112, first paragraph, is respectfully requested.

Rejection Under 35 U.S.C. §112, Second Paragraph

The examiner has rejected claims 7 and 8 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention.

In view of the amendments to claims 7 and 8 as stated above in response to the rejections under 35 U.S.C. §112, first paragraph, withdrawal of the rejections under 35 U.S.C. §112, second paragraph, is respectfully requested.

The above discussion and corresponding Amendments are based on section 112 issues and are not made to overcome art-based rejections. Accordingly, such discussion and corresponding Amendments should not be construed in a limiting manner.

It is respectfully submitted that the claims have been put in condition for allowance. Notification to this affect is earnestly solicited. The Examiner is encouraged to contact the Applicants' undersigned attorney to discuss this matter if any questions should arise upon further examination of the pending claims.

Respectfully submitted,

November 30, 2004
Date

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